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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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08/468,610

06/06/1995

SIMON C. BURTON

010055-134

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01/11/2007

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EXAMINER

WAX, ROBERT A

ART UNIT

PAPER NUMBER

1656

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/11/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

08/468,610

Applicant(s)

BURTON ET AL.

Examiner

Robert A. Wax

Art Unit

1656

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7-23, 55 and 56 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-23, 55 and 56 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

Introduction

1. This Office action is necessitated by the action of the Board of Patent Appeals and Interferences (hereinafter, "Board") in remanding the application back to the examiner and vacating all rejections of record. Since Examiner does not believe the claims to be allowable over the prior art of record, the previous rejections are restated below with elaboration as necessary. The comments of the Administrative Patent Judge (hereinafter, "APJ") will be explicitly addressed after the statement of the rejections.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-5, 7-23, 55 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection relates to the claim limitation, "further wherein about 50 percent or more of the target protein or peptide in an aqueous medium binds to the resin when the aqueous medium has either a high or low ionic strength." The claims are drawn to a resin-protein/peptide complex. This means that there is a resin that has protein or peptide already bound to it. No aqueous medium forms part of the complex and the inclusion of this limitation seems inappropriate. The phrase does not further limit the

structure or composition of the complex and, in fact, makes the claim unclear enough to be considered indefinite.

Claim Rejections - 35 USC § 102

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 3-5, 10-16, 18, 20 and 22-23 are again rejected under 35 U.S.C. 102(b) as being anticipated by Boardman et al. (1953).

A complex between an ion exchange resin and a target protein is claimed wherein the complex is formed at a pH value of between 5-9, where the resin is uncharged, and the target protein is bound to the resin by hydrophobic interactions. The ion exchange resin consists of a solid support matrix and a "selected ionizable ligand covalently attached to the matrix" (claim 1) or a "solid support matrix having a selected ionizable functionality incorporated into the backbone thereof" (claim 16).

Boardman et al. (1953) disclose separation of proteins on ion exchange media with pH elution. At low pH the cation exchange media is uncharged and binds the proteins. As the pH is raised, the protein is eluted. Figure 1(a) illustrates the technique with cytochrome C on Amberlite IRC-50 [a cross-linked poly (methacrylic acid) with a capacity of 10 Meq/g]. Amberlite IRC-50 is explicitly a "solid support matrix having a selected ionizable functionality incorporated into the backbone thereof" but at the same time, since the carboxyl functionality is covalently attached to the polymer comprising a

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chain of carbon atoms with methyl and carboxyl groups hanging off, is at the same time an "ionizable ligand covalently attached to the support matrix." At a pH value of 5, cytochrome C is tightly bound to the medium whose carboxylic groups are said to be wholly uncharged. See page 210, left column, first full paragraph ("On the other hand, as is shown in Fig. 1a, at pH 5 the carboxylic groups of the resin are almost wholly undissociated . . ."). Between pH values of 6-7 the protein elutes from the column. At the same pH range, the affinity for sodium ions increases, corresponding to an ionization of the carboxylic groups on the resin.

Claim Rejections - 35 USC § 103

6. Claims 1-5, 7-23, 55 and 56 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Boardman et al. (1953), Sasaki et al. (1979) and Sasaki et al. (1982) in view of Kunin (1958), Topp et al. (1949), Kitchener (1957) and Guthrie (1957) and further in view of Hancock et al. (US 4,401,629), Kitamura et al. (JP 01211543), Tokuyama (JP 60137441), Kondo et al. (JP 61033130), Imuro et al. (US 4,950,807), Bruegger (US 4,810,391), Economy et al. (US 3,835,072), Jones et al. (US 4,154,676).

A complex between an ion exchange resin and a target protein is claimed wherein the complex is formed at a pH value of between 5-9, where the resin is uncharged, and the target protein is bound to the resin by hydrophobic interactions. The ion exchange resin consists of a solid support matrix and a "selected ionizable ligand covalently attached to the matrix" (claim 1) or a "solid support matrix having a selected

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ionizable functionality incorporated into the backbone thereof" (claim 16). The resin may further comprise non-ionizable ligands.

The teachings of Boardman et al. (1953) have been discussed above.

Boardman et al. (1953) do not teach an exhaustive list of resins that may be used.

Sasaki et al. (1979) disclose binding several enzymes onto Amberlite CG-50 at a pH value of 4.0 where the carboxyl groups are not dissociated and, consequently, the Amberlite is uncharged. The resin can be eluted by increasing the pH so that the carboxyl groups dissociate with a concomitant loss of hydrophobicity and acquisition of a repulsive charge, which in combination decreases the binding affinity of the bound enzymes. This process of using the Amberlite ion-exchange medium is termed hydrophobic-ionic chromatography. At page 1548, the hydrophobic-ionic type of chromatography is defined as when the order of elution of proteins from the resin "is controlled by the remaining hydrophobic affinity plus the increased electrostatic affinity minus the increased electrostatic repulsion produced as the carboxyl groups are dissociated". Contrary to conventional ion exchange chromatography, enzymes bind to the uncharged functional groups and dissociate when the functional groups become charged.

The acid base titration curve of Amberlite CG-50 shown in Fig. 1 demonstrates that below a pH value of about 4.5, the resin is fully protonated and therefore should exhibit no charge. Additionally, this figure demonstrates to a person of skill in the art how to determine the effective pH range of a given resin in the hydrophobic-ionic chromatography method. That is, the titration curve shows conditions when the protein

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will be bound by hydrophobic effects, and conditions when ionic effects will dissociate the protein.

The lack of ionic strength dependence on the binding of proteins at pH 4 to Amberlite CG-50 (page 1540, column 2) and elution of proteins with organic solvents (page 1546, column 2) is further evidence that the enzymes are bound to the ion exchange matrix by hydrophobic effects. Sasaki et al. (1979) lack forming the complex with a resin that is uncharged between pH values of 5-9.

Sasaki et al. (1982) disclose binding several microbial enzymes onto Amberlite CG-50 at a pH value of 4.0 where the carboxyl groups are not dissociated and, consequently, the Amberlite is uncharged. Subsequently, elution is effected by increasing pH to ionize the resin. This overall process is termed hydrophobic-ionic chromatography (abstract). In Figure 5 a cartoon is provided to explain the proposed mechanism of hydrophobic-ionic chromatography. The cartoon clearly indicates, in general terms, that with an acidic group, binding occurs below a certain pH and desorption occurs above the critical pH. Different proteins having different interacting groups are released at different critical pH values (X or Y). This cartoon does not require any particular resin. It is a generalization of the concept of hydrophobic-ionic chromatography. The figure legend to Figure 5 clearly states, "in the case of Amberlite CG-50, X is 4.5". The figure legend continues to describe general mechanism, "with the use of appropriate adsorbent carrying alkaline groups, ... the relationship to pH would be opposite". While the cartoon illustrates the general principle with an ion-exchange resin that is acidic in nature, if the general mechanism is applied to an ion-exchange

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resin which is basic in nature, the effect of pH would be the opposite, i.e., lowering the pH would effect elution as the basic resin became charged. To understand this better, consider a resin with an amine functional group attached thereto. At sufficiently alkaline pH values, the resin is in the form of free amine and is uncharged. At lower pH values the basic amine becomes protonated to its conjugate acid and assumes a positive charge. Sasaki et al. (1982) lack forming the complex with a resin that is uncharged between pH values of 5-9.

Kunin (1958) discloses titration curves of several ion exchange media and develops some of the mathematics of describing the dissociation. The well-known Henderson-Hasselbach equation is said to fit the titration data well. Accordingly, the pKa is the pH at which the ionizable group is half titrated. Figure 13 provides titration curves for Amberlite IRC-50 (used by Boardman et al., 1953) in water and in different concentrations of KCl. The pKa in water is about 8.5 and lower in the presence of KCl. At 2 pH units below the pKa, the ionized form of an acid comprises less than 0.1% of the total acid.

Topp et al. (1949) disclose the titration of several cases of ion exchange resins. Figure 2 shows the titration with poly (methacrylic acid). In the absence of added salt, the pKa is seen to be about 8.5-9, while in the presence of 0.1 M NaCl, the pKa is lowered to about 7. In the absence of salt, exchange does not occur below pH value of 6.

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Kitchener (1957) discloses that the carboxylic acid functionality normally titrates between 7 and 11 with a midpoint of about 9, which is lowered to about 7 in the presence of 0.1N KCl (based upon the data of Topp et al., 1949).

Guthrie (1957) lists the pH at half capacity (which corresponds to a phenomenological pKa) for a number of ion exchange cotton fabrics in Table I. Several of the modifying groups have pKa values in the range of 5-9.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use ion exchange media to separate proteins where the proteins are bound at a pH value where the media is uncharged and then eluting by changing the pH to a value where the media is charged according to Boardman et al. (1953), Sasaki et al. (1979) and Sasaki et al. (1982) because media which can be used in the claimed pH range of 5-9 are known in the art as demonstrated by Kunin (1958), Topp et al. (1949), Kitchener (1957) and Guthrie (1957).

A wide range of ion-exchange media are known in the art and dozens of patents have been issued describing them, including media having the ionizable groups recited in the claims under examination. Hancock et al. (US 4,401,629) disclose polymeric ion exchange resins comprising a cross-linked vinyl backbone with attached imidazolyl groups optionally substituted with pyridyl, imidazolyl or amino groups (see abstract).

Kitamura et al. (JP 01211543), Kondo et al. (JP 61033130) or Iimuro et al. (US 4,950,807) disclose polymeric ion exchange resins having pyridyl group as the exchange group.

Tokuyama (JP 60137441) or Bruegger (US 4,810,391) disclose ion exchange resins that may have phenolic hydroxyl group as the exchange group.

Economy et al. (US 3,835,072) discloses ion exchange fibers which may have a primary, secondary, tertiary or quaternary amino group as the exchange group (column 1, lines 67-72).

Jones et al. (US 4,154,676) disclose polymeric ion exchange resins having the morpholino (column 2) group *inter alia* as the exchange group.

In sum, Boardman et al. (1953) teach a resin with binding properties in the critical region. The Sasaki et al. references were cited because they clearly disclose the concept of the instant invention. The cartoon of Figure 5 in Sasaki et al. (1982) outlines the method in its most general form. The cartoon illustrates an acidic group undergoing ionization. At low pH the proteins absorb to the uncharged resin by hydrophobic effects. As the pH is raised, the resin becomes charged and the proteins elute. The figure legend goes on to say that the method "can be used with an absorbent carrying alkaline groups, although the relationship to pH would be the opposite". That is, at high pH the resin is uncharged and the proteins bind by hydrophobic effects. As the pH is lowered, the resin becomes charged and the proteins elute. Sasaki et al. only illustrates the method with a resin that binds at pH 4.5. It is clear that their conceptualization only requires that there be resins that bind in the critical region of 5-9.

In Kunin (1958), for example, the titration curves for salt exchange were used to calculate the apparent ionization constants of some acidic resins. These are listed at page 35. In Topp et al. (1949) it is clear, for example, that the carboxyl group of

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polymethacrylate (Figure 2) undergoes salt exchange in the region of 6-9 in the absence of added salt (this is further discussed at page 3301, first full paragraph). The values for pKa can be compared to the values for pKa for suitable resins given in the instant disclosure on Tables 3 and 4 (alkaline and acid resins respectively). It would appear that suitable resins are relatively easy to obtain. The references clearly lead to using suitable resins in the allegedly critical region of pH. Such resins are clearly known in the art and reasonably suggested by Hancock et al. (US 4,401,629), Kitamura et al. (JP 01211543), Tokuyama (JP 60137441), Kondo et al. (JP 61033130), Iimuro et al. (US 4,950,807), Bruegger (US 4,810,391), Economy et al. (US 3,835,072), Jones et al. (US 4,154,676). These latter references disclose resins containing ionizable ligands as the exchange groups alleged to be suitable and specifically claimed as such in claims 55-56. Given the teachings of the art of record, it would constitute nothing more than routine optimization to select a suitable ion exchange media compatible with the target protein and having ionizable functional groups in the desired range of 5-9.

Hence, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to separate proteins with ion exchange media with a pKa value in the range of 5-9, as recited in the claims under examination.

Obviousness does not require a cookbook to follow but often includes some experimentation to determine the exact conditions to carry out a purification. Here, the general concept of the invention, hydrophobic interaction chromatography, is clearly taught by the cartoon in Sasaki et al. (1982) and the specific examples of cytochrome c and carboxyhemoglobin are taught by Boardman et al. Said person of ordinary skill

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would be able to use his or her knowledge to select the appropriate resin of the many known resins to use for purification of any specific protein.

Points Raised by the APJ

7. The APJ alleged several problems with claim interpretation, which Examiner will now address.

8. First, there is some confusion as to the difference between ionizable groups covalently attached to the resin and ionizable functionalities incorporated into the backbone of the resin. As stated above, Amberlite IRC-50® is explicitly a “solid support matrix having a selected ionizable functionality incorporated into the backbone thereof.” Clearly, since the resin is poly (methacrylic acid) and the carboxyl group is part of the molecule, the carboxyl functionality is incorporated into the backbone of the resin material. Applicants use the additional language, “selected ionizable ligand covalently attached to the matrix” so it is apparent that they want the two phrases to have different meanings. One interpretation of the latter phrase is clearly different from the former. That would be when the resin is, for example, polytetrafluoroethylene with every fourth fluorine substituted with a sulfonate group via a linker. However, this is not the only interpretation of the ionizable ligand phrase. Since poly (methacrylic acid) is a string of carbon atoms single bonded together with every other carbon atom bearing a pendant methyl group and carboxyl group. The backbone could be considered to be the carbon chain with the carboxyl being covalently attached to it and thus be described as an “ionizable ligand covalently attached to the support matrix.” Thus, while different words

are used in different claims, the two phrases are essentially duplicative and certainly not patentably distinct.

9. Next, the APJ finds an inconsistency with the pH 5-9 and electrostatic charge limitations. The specification, at page 29, lines 24-28, as pointed out by the APJ, teach that the ionizable ligands provide resins that begin to titrate (become electrostatically charged) at a pH between 5 and 9. The benefit taught by the specification is that the protein won't be exposed to a higher pH and will be less likely to denature during the purification process. Clearly, that is what happens in Boardman et al.

10. The most salient feature of Boardman is the titration curves shown in Figure 1. Clearly at pH 5.0, cytochrome C is bound, and elutes between pH values of 6-7 or 6-8 depending on ionic strength. Concomitantly, the resin takes up the sodium ions. That is, when the resin is uncharged, no sodium ions are attracted to, or taken up by, the resin.

Fig. 1a of Boardman indicates that, at pH 12, when the resin is 100% ionized, the resin can adsorb a maximum of about 8.8 mg-equivalent sodium ions/g of dry resin. See vertical scale at right hand side of Figure 1a, and the intersection with the curve represented by the broken lines. At pH 5.0, at the lower sodium concentration of 0.17 g sodium ions per liter, (curve "B"), the resin takes up about 0.4 mg-equivalent sodium ions/g of dry resin. Thus, at pH 5.0, a pH at which cytochrome C is clearly bound, the resin can take up only about 4.55% of the maximum sodium ion uptake (0.4 mg-equivalent sodium ions/gm of dry resin divided by 8.8 mg-equivalent sodium ions/g of

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dry resin times 100% = 4.55%). Therefore, given the sodium ion uptake data presented in Boardman, and contrary to the opinion evidence provided in the Becker Declaration, Boardman's Amberlite IRC 50 resin is about 4.55% ionized at pH 5.0. The fact that the theoretical total capacity of the resin is 10 meq/g, the evidence provided by the experiments conducted by Boardman et al. are more probative of what is actually happening than the fact that the uptake of the resin is less than the theoretical maximum.

In view of appellant's definition of "electrostatically uncharged" as meaning "less than 5% of the ionizable functionalities on the resin are charged" (specification, page 18), it is clear that the pH 5.0 complex between cytochrome c and Amberlite IRC 50 described by Boardman is in fact a complex between a solid support matrix having an ionizable ligand thereon and a protein, at a pH from 5 to 9, wherein the resin is electrostatically uncharged.

The specification teaches the desirability of precisely this effect, see page 29, lines 24-28. Construction of the claim limitation regarding pH and electrostatic charge is dictated by the specification and this is an excellent example of looking to the specification to provide information on how the claims should be interpreted.

11. The APJ raised the issue that the "fifty percent or more" phrase is unclear. This is addressed in the above rejection under 35 USC 112, second paragraph.

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12. The third issue raised by the APJ is the interpretation of "high and low ionic strength." The discussion on pages 11-14 of the remand goes into this in great detail. Examiner adopts the position of the APJ as his own, that is, that "high" ionic strength gives a conductivity of 4.70000000000 or greater millimho and "low" ionic strength gives conductivity less than that, i.e., from 0.00000000001 to 4.69999999999 millimho. Examiner submits that the difference between 4.69999999999 and 4.70000000000 is undetectable and, therefore, the limitation "high or low ionic strength" is meaningless. Applicants are reminded again that interpretation of claims is provided first and foremost by the specification upon which the claims are based. Applicants provided the definition and are now constrained by that definition.

13. The next issue raised by the APJ has to do with the polarity of the electrostatic charge induced on the resin be of the opposite polarity from the net electrostatic charge on the target protein at the pH of desorption. To reiterate some of the points raised, it is well established that at a pH below its pI a protein will carry a net positive charge and at a pH above its pI a protein will carry a net negative charge. In Boardman et al., the pI of cytochrome c is 10.1 and is desorbed a pH between 8 and 10 and, thus, will carry a net positive charge while the carboxyl groups on the Amberlite® will carry a net negative charge. Clearly, this is opposite polarity and meets the limitation of claim 15.

14. The last issue raised by the APJ is enablement of all aqueous media, including those containing whole cell extracts. The propriety of this claim limitation is addressed

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in the indefiniteness rejection above. Since the resin-protein complex is claimed the amount of protein in any aqueous medium is irrelevant. Examiner has "taken a step back" and considered the enablement issue and has reached the conclusion that no rejection is necessary. Page 20 of the specification addresses this issue by stating that the methods of use of the complexes are non-specific and one would expect to get some other proteins binding along with the target protein. There is also some discussion of possible pretreatments that would be expected to reduce the number of interfering proteins, all of which are well known to those of skill in the art of protein purification and would not require undue experimentation to determine how to practice the invention with any aqueous medium. In any event, the claims do not require that only the target protein be bound and since said person of skill in the art would expect at least some target protein to be bound and that another round of purification might be necessary.

Conclusion

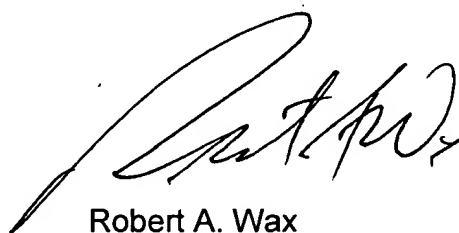
15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday from 9:00 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read 'Robert A. Wax', is positioned above the printed name and title.

Robert A. Wax
Primary Examiner
Art Unit 1656

RAW